Evaluation of the Efficacy and Safety of a Lidocaine and Tetracaine (7%/7%) Cream for Induction of Local Dermal Anesthesia for Facial Soft Tissue Augmentation with Hyaluronic Acid

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ABSTRACT

Injection of dermal fillers for soft tissue augmentation is a minimally invasive cosmetic procedure with growing popularity. However, patients often express concern about pain with such procedures. A topical anesthetic cream formulated with lidocaine/tetracaine 7%7% was approved by the United States Food and Drug Administration in 2006 and recently reintroduced to the market for use during superficial dermatological procedures. A Phase 3 study was conducted to assess the efficacy and safety of lidocaine/tetracaine 7%7% cream versus placebo cream when used to induce local dermal anesthesia during injections with hyaluronic acid. Mean visual analog scale scores significantly favored lidocaine/tetracaine 7%7% cream. A significant percent of subjects also indicated that lidocaine/tetracaine 7%7% cream provided adequate pain relief and that they would use lidocaine/tetracaine 7%7% cream again. Investigators also rated lidocaine/tetracaine 7%7% cream significantly better than placebo cream for providing adequate pain relief and on the assessment of pain scale. Lidocaine/tetracaine 7%7% cream was safe and well tolerated with most subjects reporting no erythema, edema, or blanching. No related adverse events were reported with lidocaine/tetracaine 7%7% cream; one related adverse event of erythema was reported with placebo cream. The results of this study indicate that lidocaine/tetracaine 7%7% cream is efficacious and safe at providing pain relief for soft tissue augmentation with hyaluronic acid. (*J Clin Aesthet Dermatol.* 2014;7(10):32–37.)

Soft tissue augmentation with dermal fillers is a popular, minimally invasive cosmetic procedure with an increasing number of procedures performed each year.[1] Despite the popularity of dermal filler procedures and other cosmetic procedures, most patients are concerned about the pain associated with these procedures.[2] Seventy-four percent of surveyed subjects expressed concern about associated pain with cosmetic procedures, and 42 percent of subjects who had a cosmetic procedure would consider not having other procedures due to concerns about pain.[2] These results suggest that a sizeable number of subjects are given inadequate measures to control pain during cosmetic procedures.

Various types of topical anesthetics are available to manage pain and provide relief during cosmetic procedures and contain ingredients such as lidocaine, tetracaine, and prilocaine.[3] Many physicians use compounded formulations of anesthetics to provide dermal anesthesia before a procedure. However, these products have been found to not be standardized and frequently have higher concentrations of anesthetics than United States Food and Drug Administration (FDA)-approved products.[3] This resulted in the FDA issuing a warning in 2006 to multiple pharmacies to stop compounding topical anesthetic

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creams.[4] And in 2007, a public health advisory was issued by the FDA when two women died after using compounded high-concentration topical anesthetics under occlusion before a procedure.[5] Therefore, it is recommended that only FDA-approved topical anesthetics be used as they have demonstrated efficacy as well as safety.[5]

An anesthetic cream formulated with lidocaine and tetracaine 7%/7% (LT cream; Pliaglis® Cream; Galderma Laboratories, LP) was approved by the FDA in 2006 and recently reintroduced to the market. LT cream is indicated for use on intact skin in adults to provide topical analgesia for superficial dermatological procedures.[6] In addition to being formulated with the maximum allowable FDA-approved concentrations of lidocaine and tetracaine, LT cream also dries to a flexible membrane that functions as a self-occlusive barrier. Multiple studies have demonstrated the efficacy and safety of LT cream in various dermatological cosmetic procedures including ablative and nonablative laser resurfacing, laser tattoo removal, laser hair removal, and CO_2 laser resurfacing.[7–10]

A Phase 3 study was conducted to investigate the efficacy and safety of LT cream when used as a topical anesthetic for facial soft tissue augmentation with hyaluronic acid. The results of this study indicate that LT cream provided significantly better pain relief than vehicle cream, was well tolerated, and is an ideal choice to provide topical anesthesia before dermal filler injections.

METHODS

This was a multicenter, randomized, double-blind, placebo-controlled, paired study to evaluate the efficacy and safety of LT cream when used for induction of local anesthesia for soft facial tissue augmentation with hyaluronic acid. This study was conducted in compliance with the Declaration of Helsinki, current Good Clinical Practice guidelines, and any other applicable regulations. The protocol was approved by an institutional review board, and all subjects gave written informed consent before participating in the study.

Subjects, treatments, and assessments. Men and women over the age of 18 years who had elected to undergo dermal filler injections in the face were eligible for enrollment. Any subject who had a known allergy, sensitivity, or contraindication to lidocaine or tetracaine was excluded.

Subjects were randomized 1:1 to receive LT cream on either the top/right or left/bottom treatment area and vehicle cream on the alternate treatment area (defined as two similar anatomical locations that required similar amounts of filler). LT cream and vehicle cream were concurrently applied for 30 minutes to the designated treatment areas in a uniform thickness of approximately 1mm. After removal of the cream, the area was evaluated by the investigator for signs of erythema, edema, blanching (each assessed on a 5-point scale) or any other skin reactions. Subjects then received injections of hyaluronic acid (Restylane®, Medicis Aesthetics Inc.) on the top/right area first, followed by the bottom/left area second.

TABLE 1. Subject demographics

	SUBJECTS
Enrolled, n	70
Completed, n (%)	70 (100)
Mean Age, y (SD)	50.5 (8.9)
Gender, n (%)	
Male	67 (96)
Female	3 (4)
Race, n (%)	40 (52.6)
Caucasian	66 (94)
Hispanic	1 (1)
African American	1 (1)
Other	2 (3)
Skin Type, n (%)	
I	5 (7)
II	12 (17)
III	31 (44)
IV	14 (20)
V	7 (10)
VI	1 (1)

The primary efficacy variable was the subject's evaluation of pain using a visual analog scale (VAS) from 0mm (no pain) to 100mm (the worst pain you can imagine). Each subject completed two VAS (1 per treatment) after the injections. Secondary efficacy variables included subject and investigator evaluations. Subjects were asked if they felt LT cream or vehicle cream provided adequate pain relief and if they would use either cream again if given the option (both were yes/no questions). Investigators were asked if they felt LT cream provided adequate anesthesia

TABLE 2. Overview of treatments administered		
	TREATMENT	
	LT CREAM	VEHICLE CREAM
Mean duration of application, min (SD)	30.3 (0.6)	30.3 (0.6)
Mean application area, cm^2 (SD)	13.2 (5.6)	13.2 (5.6)
Mean number of hyaluronic acid injections, n (SD)	4.77 (2.09)	4.79 (2.08)
Mean amount of hyaluronic acid injected, mL (SD)	0.44 (0.15)	0.46 (0.15)

for the procedure (yes/no question). Investigators also assessed subject pain intensity on a scale from 0 (no pain) to 3 (severe pain). The subject and investigator were blinded to each other's reports.

All adverse events (AEs) were recorded during the study. Subjects were contacted by telephone 20 hours to 72 hours after application of LT cream to question about their application sites for signs of delayed skin reactions.

Statistical analysis. The primary analysis of efficacy was a paired *t*-test of VAS scores to compare treatments. An exploratory analysis of the VAS scores was conducted and was an analysis of variance; pairwise comparisons of centers and comparison of treatments within each center were done using least squares mean. An exact McNemar test was used for analysis of secondary efficacy variables. All statistical tests were 2-sided and had a significance level of 0.05. There was no adjustment for multiplicity and missing data were treated as missing for all analyses. Demographics, other baseline data, and safety data were summarized descriptively.

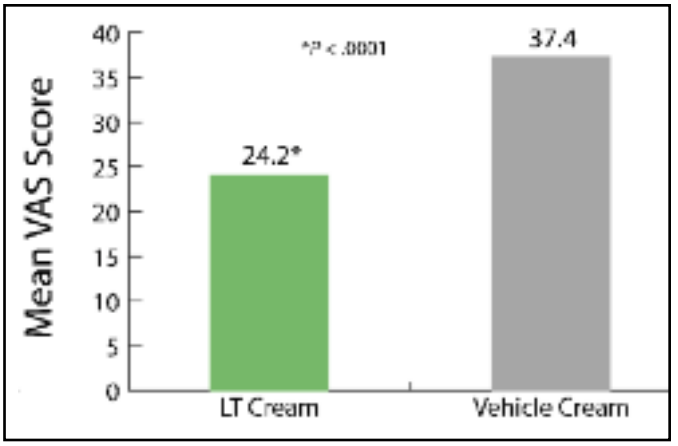

Figure 1. LT cream provided significantly better pain relief than vehicle cream as measured by the VAS.

RESULTS

Seventy subjects were enrolled at three study centers, and all subjects completed the study (Table 1). Most subjects were Caucasian women and the study group had a mean age of 50.5 years. Over half of subjects had a skin type of II or III.

Application area and duration was identical between LT cream and vehicle cream (Table 2). The amount of hyaluronic acid injected and the number of injections was similar between LT cream and vehicle cream. Subjects had an average of 4.77 injections and an average total of 0.44mL of hyaluronic acid injected on the area treated with LT cream. An average of 4.79 injections and an average of 0.46mL were injected in the area treated with vehicle cream.

The mean VAS score significantly favored LT cream over vehicle cream ($P<0.0001$; Figure 1). No statistical difference was found between treatment centers, between sides, or sequence of application (i.e., LT cream first or vehicle cream first; data not shown).

Significantly more subjects felt LT cream provided adequate pain relief compared to vehicle cream ($P=0.0052$; Figure 2), and significantly more subjects would use LT cream again compared to vehicle cream ($P=0.0094$; Figure 3).

The investigators rated LT cream as providing adequate anesthesia more often than vehicle cream ($P=0.0013$; Figure 4). The investigator assessment of pain also significantly favored LT cream with 83 percent rated as 0 (no pain) or 1 (slight pain) compared to just over half (53%) of vehicle cream rated as 0 or 1 ($P=0.0013$; Figure 5).

LT cream was well tolerated and safe in this study. Tolerability was similar between LT cream and vehicle cream (Table 3). Most subjects had no erythema, no edema, and no blanching with either treatment. Sixteen subjects experienced an adverse event during the study. One adverse event of erythema was considered related to

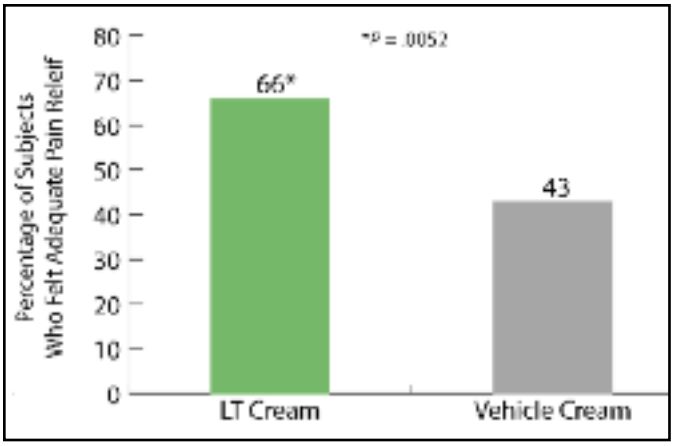

Figure 2. Significantly more subjects felt LT cream provided adequate pain relief compared to vehicle cream.

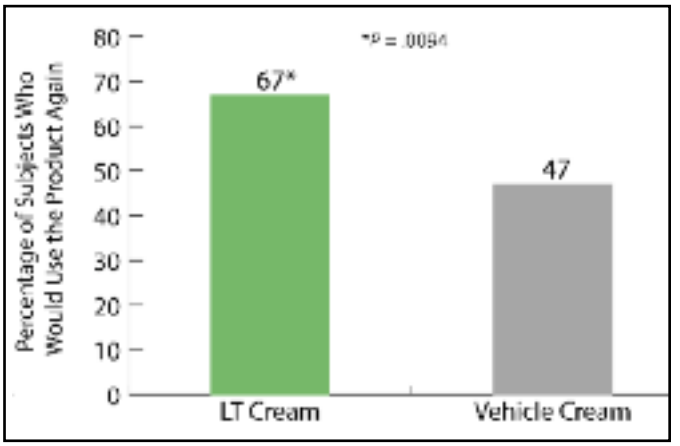

Figure 3. Significantly more subjects would use LT cream again compared to vehicle cream.

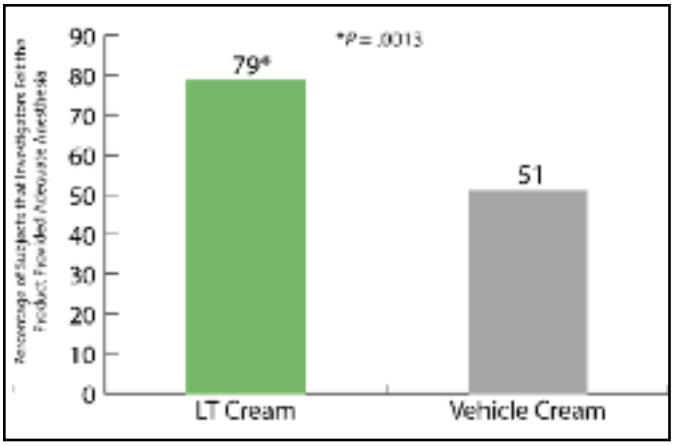

Figure 4. Investigators rated a significantly higher percentage of subjects as having adequate anesthesia with LT cream.

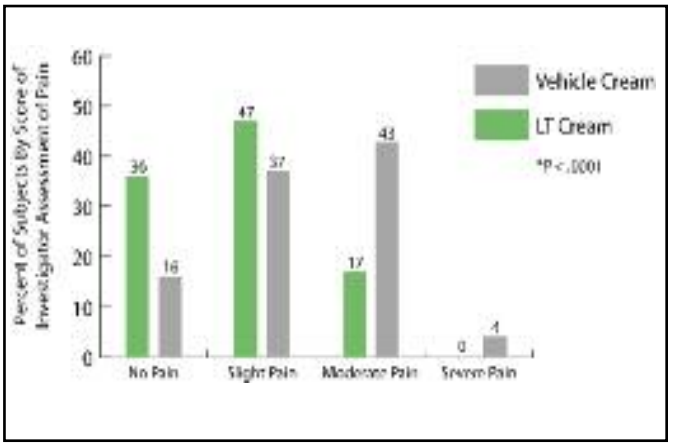

Figure 5. Investigators rated LT cream significantly better than vehicle cream on the assessment of pain scale.

vehicle cream by the investigators (Table 3). No related adverse events were reported for LT cream.

DISCUSSION

The results of this study indicate that LT cream is effective at providing adequate pain relief for soft facial tissue augmentation procedures. LT cream was rated better than vehicle cream by subjects and investigators, and a majority of subjects also indicated they would use LT cream again. LT cream was also well tolerated and no related adverse events were reported.

These results are similar to previously published studies of LT cream involving other cosmetic procedures.[7–10] However, most of these studies involved procedures with lasers. The present study demonstrates the utility of LT cream in procedures other than those with lasers, specifically efficacy in soft-tissue augmentation of the face. For many subjects, it seems the "initial prick" with the needle is of more concern than the actual injection of product into the skin. Thus, use of LT cream can help mitigate that fear through topical anesthesia. Furthermore, newer formulations of hyaluronic acid that were released subsequent to this study incorporate lidocaine, which may provide additional relief after the initial needle stick.

In light of the FDA warnings in 2006 and 2007, it is imperative that only anesthetic products with demonstrated safety be chosen for use. Compounded products may not be standardized and may contain concentrations of active ingredients that are higher than FDA-approved products.[3] These compounded products also frequently lack warnings as well as specific instructions for use. Multiple over-the-counter products (OTC) are available that contain lidocaine, but OTC concentrations are lower than allowable prescription concentrations.[11] Although LT cream requires in-office application and waiting for subsequent topical anesthesia, this is advantageous over allowing patients to self-apply products at home before coming to the office due to the associated safety risks.

The other available prescription product is a cream

TABLE 3. LT cream tolerability and safety

	LT CREAM	VEHICLE CREAM
Erythema, n (%)		
None	44 (63)	45 (64)
Very slight	16 (23)	17 (24)
Well defined	10 (14)	8 (11)
Moderate to severe	0 (0)	0 (0)
Severe to slight eschar formation	0 (0)	0 (0)
Edema, n (%)		
None	59 (84)	63 (90)
Very slight	8 (11)	3 (4)
Slight	3 (4)	4 (6)
Moderate	0 (0)	0 (0)
Severe	0 (0)	0 (0)
Blanching scale, n (%)		
None	57 (81)	66 (94)
Slight, diffuse blanching with indistinct outline	13 (19)	4 (6)
More intense blanching with half of the treated site perimeter outlined	0 (0)	0 (0)
Marked blanching with a distinct outline of the treated site	0 (0)	0 (0)
Extreme blanching with a distinct outline of the treated site	0 (0)	0 (0)
Related adverse events, n (%)	0 (0)	1 (1)
Erythema, n (%)	0 (0)	1 (1)

formulated with lidocaine and prilocaine 2.5%/2.5% (LP Cream; EMLA® Cream, AstraZeneca). LP Cream has been demonstrated to be effective and safe.[12–15] However, in a comparative trial between LT cream and LP cream (applied for 30 minutes) for topical anesthesia before ablative laser resurfacing, VAS scores significantly favored LT cream over LP cream, and significantly more subjects said they would use LT cream again versus LP cream.[10] Thus, LT cream may provide better pain relief than other safe and FDA-approved options currently on the market.

In summary, the results of this trial indicate that LT cream provides effective pain relief for facial soft tissue augmentation with hyaluronic acid injections. The ease of application and removal, as well as its effectiveness in recent clinical trials, make LT cream an ideal choice for dermal filler injection procedures as well as other minimally invasive dermatological and cosmetic procedures.

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